Inhibition of miR-25 improves cardiac contractility in the failing heart.

Journal: Nature

Publication Year: 2014

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PubMed link: 24670661

Funding Grants: Chemical Genetic Approach to Production of hESC-derived Cardiomyocytes

Public Summary:
Heart failure is characterized by a debilitating decline in cardiac function, and recent clinical trial results indicate that improving the contractility of heart muscle cells by boosting intracellular calcium handling might be an effective therapy. MicroRNAs (miRNAs) are dysregulated in heart failure but whether they control contractility or constitute therapeutic targets remains speculative. Using high-throughput functional screening of the human microRNAome, here we identify miRNAs that suppress intracellular calcium handling in heart muscle by interacting with messenger RNA encoding the sarcoplasmic reticulum calcium uptake pump SERCA2a (also known as ATP2A2). Of 875 miRNAs tested, miR-25 potently delayed calcium uptake kinetics in cardiomyocytes in vitro and was upregulated in heart failure, both in mice and humans. Whereas adeno-associated virus 9 (AAV9)-mediated overexpression of miR-25 in vivo resulted in a significant loss of contractile function, injection of an antisense oligonucleotide (antagomiR) against miR-25 markedly halted established heart failure in a mouse model, improving cardiac function and survival relative to a control antagomiR oligonucleotide. These data reveal that increased expression of endogenous miR-25 contributes to declining cardiac function during heart failure and suggest that it might be targeted therapeutically to restore function.

Scientific Abstract:
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